Bile acids are synthesized from cholesterol in the liver where they play essential roles in assisting the intestinal absorption of fats and fat-soluble vitamins as well as in eliminating excess cholesterol and promoting bile flow. Bile acid synthesis disorders are generated by mutations of specific genes which cause irregularities in the production of bile acids. Deuterated lithochol-5-enoic acid (1), chenodeoxychol-5-enoic acid (2) and chol-5-enoic acid (3) are known quantitative standards for mass spectroscopy studies and we recently required gram quantities of these analogs containing a minimum of 3 deuterium atoms per compound (+3 AMU). Although synthetic routes to 1-3 are known it proved extremely challenging to achieve both reliable D incorporation and sufficient purity for our needs using these methodologies.

Here we report an improved synthetic approach to 1 and 2 that allowed us to obtain these deuterated bile acids on gram scale with high regioselectivity and stereoselectivity, excellent chemical purity and with a high percentage of incorporation of at least three deuterium atoms. Extensive and detailed NMR studies were conducted to fully characterize the incorporation of labeled atoms into the targeted bile acid frameworks. We further report a novel synthesis of deuterated acid 3 based upon a stereoselective copper catalyzed allylic benzoyloxylation reaction to install the 7-hydroxy functionality. Again, this approach gave both a good chemical yield and reliable deuterium incorporation.